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Acute Promyelocytic Leukemia After Treatment for Non-Hodgkin's Lymphoma With Drugs Targeting Topoisomerase II

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We report a patient who developed acute promyelocytic leukemia (APL) concomitantly with a second relapse of non-Hodgkin's lymphoma (NHL), intermediate grade, WF type E. At diagnosis and at first NHL relapse, the patient had received the same chemotherapy regimen, which included drugs targeting DNA topoisomerase II, i.e., etoposide (total dose 5,760 mg) and idarubicin (total dose 180 mg). Thirty-eight months after initial treatment, the patient showed pancytopenia associated with lymphoma recurrence. Bone marrow examination revealed the presence of atypical promyelocytes with Auer rods; cytogenetics showed t(15;17), and molecular analysis detected promyelocytic leukemia-retinoic acid receptor alpha rearrangement. APL reached complete remission after all *trans* retinoic acid therapy, whereas NHL did not respond to further chemotherapy. In the literature, five other patients developed APL after treatment for lymphoma, from a total of 59 patients developing sAPL after treatment for any type of neoplasia. Am. J. Hematol. 60:300–304, 1999. © 1999 Wiley-Liss, Inc.

Key words: APL; NHL; etoposide; idarubicin

INTRODUCTION

The occurrence of acute promyelocytic leukemia (APL) after treatment of a preceding malignancy (sAPL) is a rare event. Indeed, APL constitutes 10% of all acute myeloid leukemias (AML) but only 2.7% of therapy-related AML (sAML) [1]. It has been suggested that agents targeting DNA topoisomerase II may be responsible for sAPL [2,3]. We report the case of a woman treated with regimens including agents targeting topoisomerase II for an intermediate-grade non-Hodgkin's lymphoma (NHL), who had APL simultaneously with a second relapse of the lymphomatous disease.

CASE REPORT

A 51-year-old woman was admitted in March 1993 because of hepato-splenomegaly and enlarged mediastinal and abdominal lymph nodes. Lymph node and bone marrow histology was consistent with NHL, intermediate grade, WF type E, stage IV. She entered into complete remission (CR) with six courses of the VICED regimen [4], which included vincristine (1.4 mg/m^2 on day 1), cyclophosphamide (600 mg/m^2 on day 2), idarubicin (10 mg/m^2 on day 2), etoposide (100 mg/m^2 from day 1 to day 3), and deflazacort (90 mg/m^2 from day 1 to day 5), given every 3 weeks. The patient relapsed in October 1994 with hepato-splenomegaly and enlargement of cervical, supraclavear and inguinal lymph nodes. A second remission was achieved after six additional courses of the same regimen. In May 1996, she developed hepato-splenomegaly, enlarged axillary, supraclavear and inguinal lymph nodes, and severe pancytopenia (WBC 0.5 × 10^9/L; Hb 7.9 g/dL; Plt 29 × 10^9/L). Bone marrow aspirate revealed 40% infiltration by atypical promyelocytes with giant cytoplasmatic granules and multiple Auer

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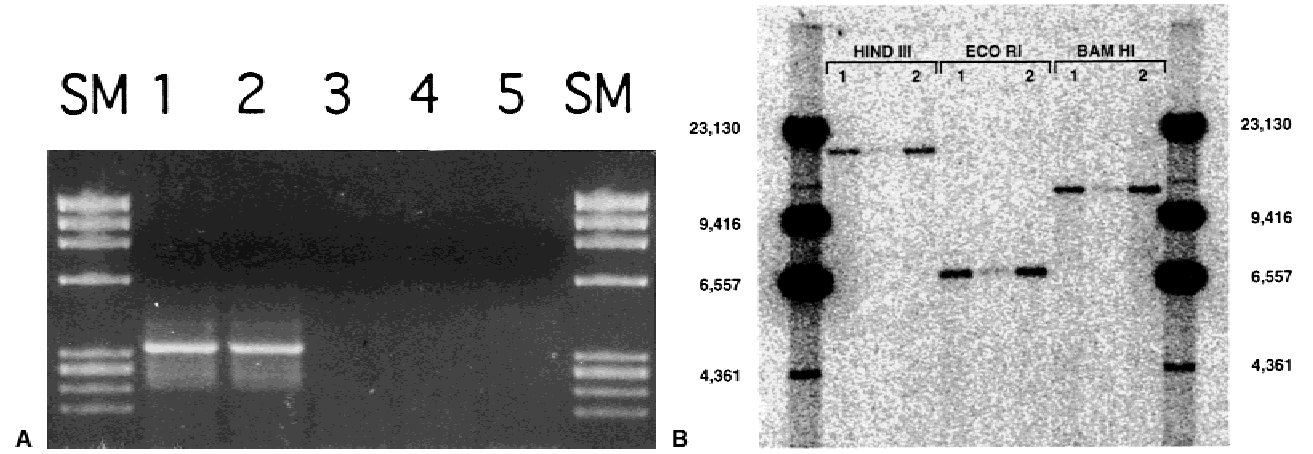

Fig. 1. (A) RT-PCR for the hybrid transcript PML-RARα. SM: molecular weight markers; lane 1: the hybrid transcript at diagnosis of APL; lane 2: ten days after starting ATRA treatment; lanes 3 and 4: four and five months after starting ATRA, showing APL molecular remission; lane 5: normal control. (B) Southern blot at diagnosis of APL, showing integrity of the fragments *Bam*HI and *Eco*RI.

rods. Cytogenetics showed the translocation t(15;17) in 15/15 metaphases; a promyelocytic leukemia-retinoic acid receptor alpha (PML-RARα) hybrid gene was detected by reverse transcriptase-polymerase chain reaction (RT-PCR) on RNA from bone marrow cells, with a BCR1 type breakpoint (Fig. 1a). The patient received a combined treatment with all *trans* retinoic acid (ATRA) (45 mg/m^2/day for 3 months) and CEOP (6 courses). She went into remission from APL, but died of lymphoma progression in November 1996 (Fig. 2).

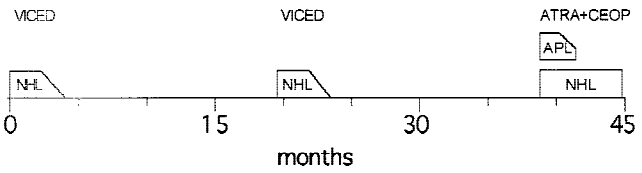

Fig. 2. Schematic presentation of the patient course, with disease-free intervals and treatment regimens.

DISCUSSION

Therapy-related AMLs constitute a subset of leukemias in which frequency is increasing. Drugs most frequently associated with sAML are alkylating agents and agents targeting DNA topoisomerase II. AML secondary to alkylating agents usually have a latency of several years (4 to 7 years) and are preceded by a dysplastic phase. They often are associated with complex karyotypic abnormalities, with frequent involvement of chromosome 5 and/or 7 [2,5] and have a poor prognosis. AML secondary to agents targeting topoisomerase II are reported with an incidence ranging from 1 to 3% [6]. They are usually characterized by a short latency (6–36 months) and absence of a preleukemic dysplastic phase. The most common chromosomal abnormalities, accounting for 30–70% of the reported cases, are balanced translocations involving 11q23 [6–8]. Other balanced alterations have been described less frequently, often similar to those observed in de novo AML, such as t(8;21) and inv16; the translocation t(15;17) accounted for 15% of these sAML [8], i.e., 2–3-fold less than those involving 11q23.

The occurrence of a balanced translocation could be related directly to the mechanism of action of the agents targeting DNA topoisomerase II: by inhibiting the reunion of the double strand breaks, these drugs may increase the risk of illegitimate recombination. The site of the breakpoint on 11q23 is found often in the region where the ALL-1 gene is located, as observed also in de novo leukemias. This region may be more susceptible to recombination because it contains several Alu repeats as well as heptamer and nonamer signal sequences for recombinase [9]. Similar molecular mechanisms may be acting in sAPL, favoring PML-RARα reunion. The risk of developing sAML has been shown to be dose and schedule dependent. As for etoposide, a total dose of more than 2,000 mg/m^2 [10] and prolonged weekly or twice-weekly administration [11] have been related to higher risk for developing sAML. At variance with sAML induced by alkylating agents, those induced by agents targeting topoisomerase II respond to chemotherapy in a way similar to de novo AML having the same cytogenetic alteration [2].

APL following treatment of NHL is rarely reported: we have collected in the literature only four cases confirmed by cytogenetic analysis [12–14], and one in which the cytogenetic study was not performed [15] (Table I). In these five cases the interval between chemotherapy

TABLE I. Cases of sAPL Following Treatment for NHL*

Sex/age	NHL type	NHL treatment	sAPL latency[a] (mo)	Cytogenetics	sAPL treatment	CR[b] (mo)	Reference
M/43	DLC	CHOP-bleo + RT	10	ND	DNR, 6MP AraC, predn	>19	Kanakura et al., 1987 [15]
M/78	DLSC	Doxo, VP16, CTX, MTX, Bleo & Predn	32	t(15;17)	DNR, AraC	12 stroke[c]	Raiker et al., 1989 [12]
F/68		CTX, vindesine +RT	30	t(15;17), −7, +4	none	NO	Detourmignies et al., 1992 [13]
M/23		High dose MTX & AraC	30	t(15;17)	DNR, AraC	>7	
M/60	Large cell	CHOP, PROMACE-CYTABOM	12	t(15;17)	ATRA	>9	Pogliani et al., 1995 [14]
F/51	DSCC	VICED	38	t(15;17)	ATRA, CEOP	6 NHL[c]	Present report

*APL, acute promyelocytic leukemia; NHL, non-Hodgkin's lymphoma; DLC, diffuse large cell; CR, complete remission; DLSC, diffuse large and small cell; DSCC, diffuse small cleaved cell; RT, radiotherapy.
[a]From the start of NHL treatment to appearance of APL.
[b]CR duration from APL diagnosis.
[c]Cause of death.

and APL was relatively short (10–32 months) and in three cases the preceding therapy had included agents targeting topoisomerase II. Our patient had received two drugs acting on topoisomerase II (etoposide and idarubicin), at diagnosis and after the first relapse; drug-free interval between the two treatments was about 15 months. Idarubicin was administered every 3 weeks for a total dose of 180 mg. Etoposide was administered for 3 consecutive days every 3 weeks for a total dose of 5,760 mg. APL occurred 15 months after the second treatment. This patient belongs to a series of 99 patients treated for NHL with the VICED regimen [4]; no other case of sAML has occurred in this series after a mean follow-up of 3 years.

The risk that agents targeting DNA topoisomerase II may cause sAPL is low but does exist. A total of 59 cases (60, with the present report) of APL, confirmed by cytogenetic or molecular analysis, have been reported in the literature after chemotherapy and/or radiotherapy [7,12–14,16–36]. Thirty of them were reviewed by Hoffmann et al. [16]; additional cases have been added recently. Of these 60 patients, 14 had been treated by radiotherapy alone, 14 by radio-chemotherapy, and 32 by chemotherapy alone. Of 46 patients who had received chemotherapy, 28 had been treated with regimens including epipodophyllotoxins and/or anthracyclines or anthracenedione, and 9 with dioxypiperazine derivatives (razoxane, bimolane), which are also drugs interacting with topoisomerase II, although by a different mechanism. sAPL was treated in 45 patients: 21 received chemotherapy, 15 ATRA, and nine chemotherapy combined with ATRA; 37 patients (82%) obtained complete remission. The BCR1 breakpoint, which is the most frequent in de novo APL, was identified in all the eight cases in which the fusion transcript PML-RARα was characterized [16,29,35], as well as in our case. Studying a few patients with sAPL, Naoe et al. [35] reported that in four cases in which sAPL was associated with agents targeting topoisomerase II, the BCR1 breakpoint was located in a small region of RARα intron 2 (*Eco*RI-*Bam*HI fragment), whereas in de novo APL and in one case of sAPL associated with different drugs, the breakpoint was spread in a larger area, thus suggesting that sAPL by anti-topoisomerase II may have a peculiar breakpoint. We studied by Southern blotting the breakpoint in our patient and we found normal *Bam*Hl and *Eco*RI fragments (Fig.1b). Thus, it seems that sAPL have the same clinical, morphological, cytogenetical, and molecular features of de novo APL.

In the cases collected, the interval between the preceding treatment and appearance of APL ranged from 6 to 270 months (Fig. 3). In the majority of patients the latency was 10–60 months, strongly suggesting a causal

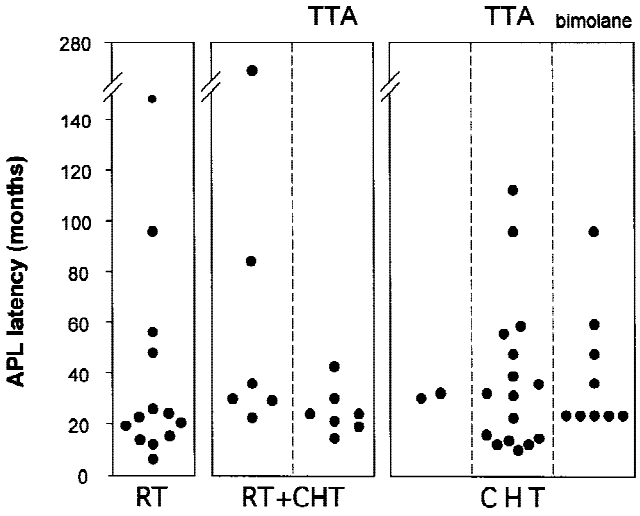

Fig. 3. Interval between treatment of the preceding neoplasia and occurrence of APL, in the published cases of sAPL (only cases with data available). TTA: chemotherapy included agents targeting topoisomerase II.

relationship between APL and the preceding treatment; in the few cases of longer latency a casual association between two neoplasms could be considered. Eighty percent of patients with post-CHT sAPL had received agents targeting topoisomerase II. Larger epidemiological studies may better assess the risk of sAPL after treatment with agents targeting DNA topoisomerase II. In any case, because patients with sAPL have a good response to therapy, they deserve the best treatment available.

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